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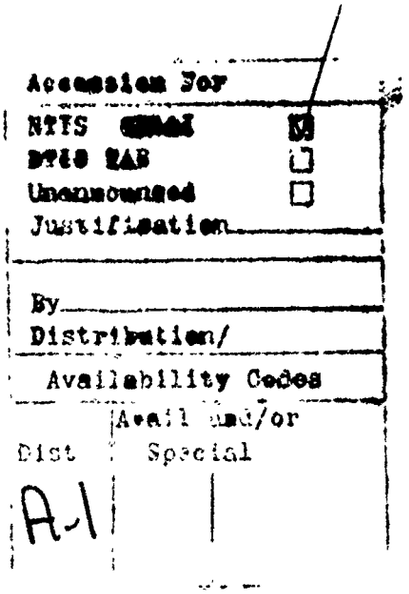

# Structural requirements for substitution on the Phe$^3$ side chain aromatic ring in a δ opioid receptor selective, cyclic tetrapeptide dermorphin analog

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## Introduction

In an effort to develop structure-activity relations for our conformationally restricted, δ-selective opioid tetrapeptide, Tyr-D-Cys-Phe-D-PenOH, electronic, lipophilic, and steric effects at the Phe$^3$ position were assessed by substitution on the side chain aromatic ring. Effects on binding were determined.

## Results and Discussion

Substitution of electronegative fluorine at the *para* position of the Phe phenyl ring (**1**) enhances δ binding affinity in the tetrapeptide, while μ binding is slightly diminished. The improved δ activity of this analog is most likely due to local electronic or lipophilic rather than conformational influences, leading to a favorable δ binding interaction. The *p*-Cl-Phe$^3$ tetrapeptide analog (**2**) was synthesized to assess further this effect, and the fluoro- and more lipophilic chloro-substituted analogs, **1** and **2**, are equiactive at the δ receptor; a slightly greater reduction is observed for **2** in μ binding affinity (three-fold relative to JOM-13). Analog **2** displays a higher affinity and index of selectivity for the δ receptor than do JOM-13 and DPDPE.

The *p*-methyl substituent in **3**, like *p*-F and *p*-Cl, is small and lipophilic but is electron-releasing rather than electron-withdrawing; this tetrapeptide modification proves detrimental to both δ and μ receptor binding. The *p*-*t*-BuPhe$^3$ analog (**4**) is the most lipophilic and bulkiest in the series. The μ binding affinity of **4** is severely compromised relative to the lead compound; negative results are also observed at the δ receptor. These unfavorable consequences can be attributed to steric effects.

In the Tyr$^3$ (**5**) and *m*-Tyr$^3$ (**6**) analogs, the hydroxyl substituent is more strongly electron-releasing than the alkyl groups above. In contrast to the lipophilic properties of the halogens and the alkyl groups, the hydroxyl moiety is hydrophilic. Again, **5** displays a reduction in opioid binding relative to the parent compound, about 14-fold at the δ receptor. This may reflect both the reduction in lipophilicity as well as a negative σ effect. It is interesting to note that the *m*-Tyr$^3$ amino acid (**6**) is better-tolerated than Tyr$^3$ (only five and 6.5-fold reductions in affinity are observed at the δ and μ receptors, respectively), likely due to differing

Table 1 *Opioid receptor binding profiles of cyclic(2–4) tetrapeptides; Phe³ residue aromatic substitution*

| Peptide analog | Cmpd no. | Binding $IC_{50}$ (nM) | | $IC_{50}(\mu)/IC_{50}(\delta)$ |
|---|---|---|---|---|
| | | DAMGO | DPDPE | |
| DPDPE | | 1 000 | 6.40 | 203 |
| Tyr-D-Cys-Phe-D-PenOH | JOM-13 | 182 | 2.90 | 63.0 |
| Tyr-D-Cys-*p*FPhe-D-PenOH | 1 | 274 | 1.65 | 166 |
| Tyr-D-Cys-*p*ClPhe-D-PenOH | 2 | 556 | 1.56 | 356 |
| Tyr-D-Cys-*p*MePhe-D-PenOH | 3 | 2980 | 8.64 | 345 |
| Tyr-D-Cys-4-*t*BuPhe-D-PenOH | 4 | >10 000 | 58.7 | >170 |
| Tyr-D-Cys-Tyr-D-PenOH | 5 | 6550 | 41.0 | 160 |
| Tyr-D-Cys-*m*Tyr-D-PenOH | 6 | 1210 | 14.9 | 81.2 |
| Tyr-D-Cys-*p*$NO_2$Phe-D-PenOH | 7 | 233 | 2.66 | 87.6 |

DAMGO = [³H][D-Ala², NMePhe⁴, Gly⁵-ol]enkephalin
DPDPE = [³H][D-Pen², D-Pen⁵]enkephalin

electronic features of the aromatic ring resulting from *meta* rather than *para* substitution. In fact, a *meta* hydroxyl group has a positive $\sigma$ value.

Introduction of a *para* nitro substituent on the Phe aromatic moiety in both linear [1] and cyclic [2] $\mu$-selective dermorphin-related tetrapeptides induces a sharp decline in $\mu$ binding affinity. However, the *p*-$NO_2$Phe³ (7) substitution does not affect $\mu$ or $\delta$ activity. While these results may appear inconsistent, the observation that affinity is not compromised fits the general trend observed for this group of analogs. Specifically, the nitro group has a high positive $\sigma$ value (a favorable contribution) since it is electron-withdrawing, and a *p*-nitro moiety enhances lipophilicity. However, the large molecular volume of the nitro substituent may lead to an adverse steric effect at the receptor; these properties may neutralize one another.

These effects are generally consistent with reports of analogous modification in the linear pentapeptide enkephalins [1,3–7] and DPDPE [6,8–10] where data are available. Data for this group of modifications imply that while steric, lipophilic, and electronic effects all play a role in influencing binding interactions at this residue, the most important determinant for opioid activity appears to be the electron-withdrawing property of the substituent. In general, those substituents possessing a positive $\sigma$ value enhance activity, while those with a negative $\sigma$ value, those lacking lipophilic character, or those possessing larger van der Waals radii decrease binding.

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